REMARKS:

The Examiner's Office Action has been reviewed and considered.

Obviousness

Responding the Final Office Action filed July 6, 2004 an amended set of claims where claim 1 reads as follows:

1. A composition for lowering serum cholesterol level in human subjects, said composition comprising one or more primary aliphatic alcohol fatty acid ester, wherein the fatty acid contains 4 to 22 carbon atoms.

The Examiner agreed that this claim have addressed satisfactorily all the previous reasons for rejection which were consequently whitdrawn. (See Office Action of 9/22/2004 at pages 2-3)

Nevertheless, in the same document, the Examiner rejects the above claim and all subsequent claims based on 35 U.S.C. 103(a), that is an obviousness rejection. The line of reasoning leading to the rejections appears to be that free policosanols and some free fatty acids, notably linoleic acid are known for their hypocholesterolemic effect, and that the claimed invention merely combines chemically these compounds in an ester form. Quoting from the Examiner's Office Action:

> "Furthermore, the esters herein having two moieties, the preferred policosanol and linoleic acid, or EPA or DHA, would be hydrolyzed within the body (in vivo) by cleaving the ester bond to regenerate two active drugs , the policosanool and linoleic acid or EPA or DHA, based on the well known teachings of esters as prodrugs in pharmaceutical art according to Bundgaard." (emphasis in original)
>
> Therefore, one of ordinary skill in the art would have reasonably expected that conjugating the policosanol such as tetracosanol, hexacosanol, octacosanol or triacontanol with a fatty acid such as linoleic acid or EPA or DHA, into an ester in a

> composition to be administered, and the ester regenerating the policosanol and linoleic acid or EPA or DHA in the body, both known useful for the same purpose, i.e. treating hypercholesterolemia, would improve the therapeutic effects for teating the same disorder, hypercholesterolemia, and or would produce additive therapeutic effects in treating the same. It is considered prima facie obvious to combine two active composition components into a single composition to form a third composition useful for the very same purpose."

9/22/2005 Office Action, pages 6-7

In summary the Examiner argues that the invention would have been obvious due to:

a) Policosanol esters are cleaved within the body leading to a mixture of free policosanols and free fatty acids and each of these, separately, are known hypocholesterolemic agents;

b) Within the body they would produce additive therapeutic effects;

c) All the above was known by the skilled artisan at the time the invention was made,

d) Ergo, the invention would have been obvious to the skilled artisan.

Applicant believes that the Examiner's reasoning is fatally flawed because neither a) nor b) are truisms or statements of an obvious truth.

With respect to a), certainly there are many esters, specially those commonly found in the diet, such as triglicerides, sterol esters and others which are cleaved by the pancreatic lipases. Some esters where one of the moiety in the molecule is either a lower alcohol (metanol or ethanol) or a lower fatty acids (formic or acetic) do not require enzymatic cleavage because they are hydrolized by the highly acidic gastric juices.

But there are other esters which are not cleaved by neither of the above mechanisms, Bundgaard notwithstanding. Surely, the skilled artisan should have been aware, at the time our invention was made, of the well known case of Olestra and the story of its development. Olestra is the generic name for sucrose esters of fatty acids. It was developed by Procter & Gamble (trade name Olean). Its intended use was as ingredient in a substitute of mother milk under the assumption that the compound once hydrolized within the body would generate sucrose and fatty acids, essential nutrients for infants. To the surprise of the researchers, Olestra, as turned out, was neither digested nor absorbed; that is, it was not cleaved by the pancreatic lipases, and passed through the body unchanged. Today, Olestra, due to this very fact, is used as a non-caloric substitute for oils and fats. In hindsight, the non digestibility of Olestra is not too surprising given that it is a synthetic ester not found in dietary sources.

Policosanols esters are also not found in food sources. Therefore, it is not at all prima facie obvious that they will be acted upon by pancreatic lipases. Another interesting and surprising feature of Olestra, is that it also has a small effect on reducing blood levels of cholesterol, an effect neither sucrose nor most fatty acids have.

In consequence, in view of Olestra and the fact that policosanol esters of the invention are also synthetic esters not found in most food sources, it would have been and it is far from obvious that said esters are hydrolized by the pancreatic lipases to form free policosanols and free fatty acids. The non obviousness of the hypocholesterolemic effect of policosanol esters follows naturally.

Once it has been shown that a) is not a truism, argument b) becomes irrelevant to the obviousness inquiry. Nevertheless, it is believed that the Examiner is wrong to assume that point

b) above is true. In the pharmaceutical art not a single case is known wherein the therapeutic effects of two drugs are additive. That would mean that, for example, drug A at a certain dosage lowers blood levels of cholesterol in 15 % and drug B does the same by 10 % then by taking both drugs blood levels of cholesterol would be lowered by 25 %. This is the true meaning of additivity. We think, that what probably the Examiner had in mind was synergism which means that two or more drugs work together to produce an effect greater than the individual effects of the component drugs. Synergism by itself is often the basis for a finding of patentability, because it is not a prima facie obvious effect.

Skilled artisans are aware that drug interaction can be divided in four groups: antagonism, synergism, potentiation and interaction with metabolism. The effect of taking two o more drugs together is always found either by accident or through systematic research. Obvious is not at all clear when the mechanism of action and/or the metabolism of the drugs is not known as in the case of policosanols. It is also not known what mechanism of action of linoleic acid lowers blood cholesterol levels.

That is, even assuming that policosanols esters are cleaved in the body (a nonobvious effect as we have seen above) it is not *prima facie* obvious that there would be synergism or potentiating effect between them. What if they were antagonistic? Therefore it is not "prima facie obvious to combine two active composition components into a single composition to form a third composition useful for the very same purpose." Such combinations arise from long term research.

It is Applicant's belief that this application is in a condition for allowance. An action so indicating is respectfully requested. If the Examiner believes that discussion of this application would be beneficial, the undersigned may be contacted at the telephone number stated below.

Applicant has submitted a separate request for a three month extension for the submission of this Resposne. You are hereby authorized to deduct from our Deposit Account, No. 02-0400 (Baker & McKenzie) the appropriate amount. When identifying such a withdrawal, please use our Attorney Docket No. HAR-104.

March 18, 2005

Respectfully submitted,

David I. Roche
Reg. No. 30,797

BAKER & McKENZIE LLP
130 E. Randolph Drive
Chicago, IL 60601
ph: +1 312 861 8608
fax: +1 312 698-2363
email: David.I.Roche@Bakernet.com